



# Acute systemic reactions to sublingual immunotherapy for house dust mite

To the Editor,

Sublingual immunotherapy (SLIT) is a successful treatment of allergic rhinoconjunctivitis by inducing clinical and immunological tolerance.<sup>1</sup> Compared to subcutaneous immunotherapy (SCIT), severe adverse reactions to SLIT are less frequently seen.<sup>2</sup> In 2017, treatment with SQ house dust mite sublingual immunotherapy tablets (hereinafter: SQ-HDM) has been registered in many European countries. In this letter, we describe two patients with acute systemic adverse reactions after administration of SQ-HDM. See Table 1 for patient characteristics. Both events occurred in our outpatient clinic.

Patient 1 was a 35-year-old female with persistent allergic rhinoconjunctivitis due to HDM allergy, which was serologically confirmed (Table 1). Furthermore, she was known to suffer from moderate allergic asthma, well controlled with fluticasone/salmeterol (Seretide 250/25 µg/dose b.i.d.) and salbutamol inhalations (Salbutamol 100 µg/dose if necessary q.i.d.) without airflow obstruction (see pulmonary function testing in Table 1). Due to uncontrolled allergic rhinitis, despite nasal corticosteroids (Azelastine/Fluticasone Nasal Spray 137/50 µg per actuation) and antihistamines (Levocetirizine 5 mg b.i.d.), immunotherapy with SQ-HDM was initiated. She never had treatment with SCIT previously. She received her first treatment with SQ-HDM in September. At the time of administration, routine questioning confirmed that she was in a good clinical condition without any signs of current infections, respiratory tract symptoms, oral lesions, emotional stress, or sleep deprivation and the administration of SQ-HDM was not during her menstrual period. Within 5 minutes after sublingual administration of SQ-HDM, she experienced dizziness, shortness of breath, and feeling of thick throat. Examination showed a blood pressure of 161/88 mmHg, a tachycardia of 150 beats per minute (an electrocardiogram showed sinus tachycardia without other abnormalities). Her temperature was 37.2°C, oxygen saturation of 100% without oxygen therapy, and she was breathing 16 times per minute. There were no signs of urticaria, and no swelling of the tongue or lips was observed (nasopharyngoscopy was not performed). Diffuse muscle fasciculations were observed without signs of rough myoclonus. She was stabilized and treated with adrenalin 0.5 mg intramuscularly and clemastine 2 mg intravenously. After treatment, the symptoms disappeared within an hour. She was admitted for a short period of observation. Serum tryptase level 1-2 hours after the event was 3.30 µg/L (ref: 0.00-11.4).

Patient 2 was a 19-year-old female with refractory rhinoconjunctivitis with allergy to tree pollen, grass pollen, and HDM, confirmed serologically (Table 1) as well as by a skin prick test. She declined SCIT; therefore, treatment with SQ-HDM was initiated in September. She has not been treated with immunotherapy in the past. She confirmed specifically that she was in a good clinical condition without any signs of current infections, respiratory tract symptoms, oral lesions, emotional stress, or sleep deprivation, and the administration of SQ-HDM was not during her menstrual period. Within 3 minutes after sublingual administration, she experienced a feeling of thick throat, shortness of breath, dizziness, and excessive vomiting. Her vital signs showed a blood pressure of 109/86 mmHg, a tachycardia of 96 per minute, and oxygen saturation of 96% without oxygen therapy, and she was breathing 16 times per minute. She was stabilized and treated with adrenalin 0.5 mg and clemastine 2 mg intramuscularly. Serum tryptase level measured 1-2 hours after reaction was 4.90 µg/L (ref: 0.00-11.4). After 4 hours of observation, she was discharged in a good condition.

Acute severe adverse reactions to SQ-HDM have been described sporadically.<sup>3</sup> To our best knowledge, only 1 case of anaphylaxis to SQ-HDM and 4 cases of systemic reactions to grass SLIT have been reported.<sup>3,4</sup> However, physicians need to be aware of these reactions and should be able to stabilize a patient with an acute reaction.

Both patients showed symptoms of a systemic reaction which occurred immediately after sublingual administration of SQ-HDM. According to the World Allergy Organization (WAO) systemic allergic reaction grading system, both patients had a grading score of 3.<sup>5,6</sup> Even though grade 3 is not defined as anaphylaxis by WAO, anaphylaxis cannot be ruled out, because this is a clinical diagnosis. The observation that serum tryptase 1 to 2 hours after the start of the reactions was low, does not exclude an IgE-mediated reaction.<sup>7</sup>

Several risk factors have been described for developing systemic reactions, such as decreased lung function, oral lesions, concurrent infections, or emotional stress.<sup>8</sup> In our patients, none of these risk factors could be identified. Patient 1 was known with rhinoconjunctivitis and moderate asthma without signs of obstruction. Patient 2 only suffered from rhinoconjunctivitis and did not have symptoms of asthma. Both patients were positive for Der p2 and Der f2, but further extended molecular sensitization profile of HDM and pollens in both patients was different. The administration of SLIT took place in the month September. In autumn, exposure to

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2020 The Authors. *Allergy* published by European Academy of Allergy and Clinical Immunology and John Wiley & Sons Ltd

TABLE 1 Patient characteristics

	Patient 1	Patient 2
Gender	Female	Female
Age	35	19
Medical history	Well-controlled moderate asthma Allergic rhinoconjunctivitis due to house dust mite (HDM)	Eczema Allergic rhinoconjunctivitis due to HDM, tree pollens, and grass pollens
Lung function	VC: 3,48 liter (91% of predicted), FEV1: 2,79 liter (88% of predicted), FEV1/VC: 80%, DLCO: 78% of predicted, DLCO/VA: 84%	NA
Skin prick test	NA	Positive for HDM, tree pollens, grass pollens, and cat.
Serological test Reference kU/L: < 0.35 Reference ISU-E: < 0.30	HDM 1.64 kU/L Der f2 1.90 ISU-E Der p2 1.70 ISU-E Der p23 1.0 ISU-E	HDM 30.0 kU/L Der f2 23.70 kU/L Der f1 17.10 kU/L Der p1 10.20 kU/L Der p2 23.50 kU/L Birch pollens 48.30 kU/L Hazel pollens 15.90 kU/L Alder pollens 45.70 kU/L Oak pollens 12.20 kU/L Rye pollens 19.40 kU/L Timothy grass 25.10 kU/L Bermuda grass 35.50 kU/L Sweet vernal grass 30.00 kU/L
Medication	Levocetirizine 5 mg b.i.d. Azelastine/fluticasone nasal spray 137/50 µg per actuation. Fluticasone/Salmeterol 250/25 µg/dose b.i.d. Salbutamol inhalations 100 µg/dose if necessary q.i.d.	Fluticasone furoate 27,6µg q.d. Levocetirizine 5 mg b.i.d.
Symptoms during acute reaction to SQ-HDM	Dizziness, tachycardia, feeling of thick throat, dyspnea	Itchy mouth, dizziness, feeling of thick throat, dyspnea, excessive vomiting.
Hemodynamics	Blood pressure: 161/88 mmHg Pulse: 150 beats/min Temperature: 37.2°C Saturation: 100% without oxygen therapy Breathing: 16 times/min	Blood pressure: 109/86 mmHg Pulse: 96 beats/min Saturation: 96% without oxygen therapy Breathing: 16 times/min.
Treatment	Adrenalin 0.5 mg IM Clemastine 2 mg IV	Adrenalin 0.5 mg IM Clemastine 2 mg IV
Serum tryptase 1-2 h after reaction	3.30 µg/L (ref: 0.00-11.4)	4.90 µg/L (ref: 0.00 - 11.4)

HDM in the Netherlands is higher than in spring.<sup>9</sup> However, there are no studies showing that the onset of immunotherapy administration with HDM should be determined by seasonal variation in HDM exposure.

In conclusion, acute systemic reactions to SQ-HDM may occur. Awareness is important, and patients should be monitored appropriately after taking SQ-HDM.

#### CONFLICT OF INTEREST


Dr Janssens has nothing to disclose. Dr van Ouwkerk has nothing to disclose. Dr Gerth van Wijk reports personal fees from ALK Abello, outside the submitted work. Dr Karim has nothing to disclose.


#### KEYWORDS

sublingual immunotherapy, house dust mite, adverse event, allergy

Nicky S. Janssens<sup>1</sup>

Lotte van Ouwkerk<sup>1</sup>

Roy Gerth van Wijk<sup>2</sup> 

Faiz Karim<sup>1,2</sup> 

<sup>1</sup>Department of Internal Medicine, Groene Hart Hospital, Gouda, the Netherlands

<sup>2</sup>Department of Internal Medicine, Section Allergy and Clinical Immunology, Erasmus Medical Centre, Rotterdam, the Netherlands

**Correspondence**

Faiz Karim, Department of Internal Medicine, Groene Hart Hospital, bleulandweg 10, 2803 HH, Gouda, the Netherlands.  
Emails: faiz.karim@ghz.nl; a.karim@erasmusmc.nl

**ORCID**

Roy Gerth van Wijk  <https://orcid.org/0000-0002-9608-8742>

Faiz Karim  <https://orcid.org/0000-0001-5884-7712>

**REFERENCES**

1. Durham SR, Creticos PS, Nelson HS, et al. Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: Pooled analyses. *J Allergy Clin Immunol*. 2016;138(4):1081-1088.
2. Bahceciler NN, Cobanoglu N. Subcutaneous versus sublingual immunotherapy for allergic rhinitis and/or asthma. *Immunotherapy*. 2011;3(6):747-756.
3. Blanco C, Bazire R, Argiz L, Hernandez-Pena J. Sublingual allergen immunotherapy for respiratory allergy: a systematic review. *Drugs Context*. 2018;7:212552.
4. Nolte H, Casale TB, Lockey RF, et al. Epinephrine Use in Clinical Trials of Sublingual Immunotherapy Tablets. *J Allergy Clin Immunol In Pract*. 2017;5(1):84-89.
5. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *J Allergy Clin Immunol*. 2010;125(3):569-574.
6. Cox LS, Sanchez-Borges M, Lockey RF. World allergy organization systemic allergic reaction grading system: Is a modification needed? *J Allergy Clin Immunology In Pract*. 2017;5(1):58-62.
7. Buka RJ, Knibb RC, Crossman RJ, et al. Anaphylaxis and clinical utility of real-world measurement of acute serum tryptase in UK emergency departments. *J Allergy Clin Immunol In Pract*. 2017;5(5):1280-1287.
8. Larenas-Linnemann DE, Costa-Dominguez MDC, Creticos PS. Acute emotional stress proposed as a risk factor for anaphylaxis in patients receiving allergen immunotherapy. *Ann Allergy Asthma Immunol*. 2020;124(4):314-317.
9. van der Heide S, de Monchy JG, de Vries K, Bruggink TM, Kauffman HF. Seasonal variation in airway hyperresponsiveness and natural exposure to house dust mite allergens in patients with asthma. *J Allergy Clin Immunol*. 1994;93(2):470-475.